

Appendix A: Background Information for Lead

A.1 Toxicokinetics

Gastrointestinal absorption of soluble lead salts in adult humans can be high during fasting (40–50%), but is about 3–15% when ingested with food. On the basis of dietary balance studies, gastrointestinal absorption of lead in children appears to be higher and may account for 40–50% of the ingested dose. Studies in animals also provide evidence that gastrointestinal absorption of lead is much higher in younger organisms. Absorption is strongly affected by nutritional status, with higher absorption of lead in children who are iron deficient. Calcium deficiency also may increase lead absorption, based on studies in children. Coadministration of calcium with lead decreases lead absorption in adults, and in animal studies. Vitamin D administration has been shown to enhance lead absorption in animal studies. The distribution of lead appears similar across routes of exposure. Initially, lead is distributed to the blood plasma and soft tissues, but under steady state conditions 99% of the lead in blood is found in the erythrocyte, where much of it is bound to hemoglobin. Lead accumulates in bone, such that bone lead accounts for approximately 73% of the body burden in children, increasing to 94% in adults. Inorganic lead is not known to be metabolized, but lead ions are complexed by macromolecules. Unabsorbed lead is excreted in the feces; absorbed lead that is not retained is excreted through the urine and bile (ATSDR 1999b).

A.2 Health Effects

The effects of lead are similar across inhalation and oral routes of exposure. Lead has been shown to affect virtually every organ and system in the body in both humans and animals. The most sensitive effects of lead appear to be neurological (particularly in children), hematological, and cardiovascular. Epidemiological studies provide evidence for an association between prenatal and postnatal exposure to lead and adverse effects on neurodevelopment in infants and young children, and support the use of PbB as an index of toxicological effect. The neurological effects included impaired cognitive ability and IQ deficits in children. On the basis of several meta-analyses, it appears that a highly significant IQ decrement of 1–3 points is associated with a change in PbB from 10 to 20 µg/dL. In addition, associations between biomarkers of lead exposure and increased problem behavior in the classroom have been reported (ATSDR 1999b; Marlowe et al. 1985a). In adult humans, slowing of nerve conduction velocity occurs at PbBs of 30 µg/dL; peripheral nerve function appears to be affected in children at similar PbBs. Oral studies in animals support the human evidence regarding neurobehavioral toxicity of

lead to infants and children from prenatal and postnatal exposure. In animals, lead has been shown to alter a number of neurotransmitter systems including dopamine, norepinephrine, serotonin, and gamma-aminobutyric acid systems (ATSDR 1999b).

Lead interferes with the synthesis of heme, resulting in accumulation of ALA in tissues and elevated excretion of ALA in urine, elevation of zinc protoporphyrin in erythrocyte, reductions in blood hemoglobin, and in a hypochromic, normocytic anemia at higher levels of exposure. Many epidemiological studies have found increases in blood pressure to be associated with increases in PbB. The contribution of lead, as compared with other factors, is relatively small, and whether the observed associations represent causality is controversial. Animal data demonstrate that oral exposure to lead increases blood pressure. At higher levels of exposure in humans, lead produces cardiac lesions and electrocardiographic abnormalities. Chronic nephropathy in humans is associated with PbB levels of 40–>100 µg/dL. Oral exposure of animals to lead causes renal damage; histopathology is similar in humans and animals and includes intranuclear inclusion bodies, swollen mitochondria, and tubular damage. Adverse effects on the testes and sperm have been seen in occupationally exposed men with PbBs of 40–50 µg/dL, and the more recent literature suggest that PbB concentrations <40 µg/dL also may be associated with adverse effects on sperm counts and morphology (ATSDR 1999b).

A.3 Mechanisms of Action

Lead can affect virtually every organ or system in the body through mechanisms that involve fundamental biochemical processes. These mechanisms include the ability of lead to inhibit or mimic the action of calcium and to interact with proteins. In the interaction with proteins, lead binds with virtually every available functional group, including sulfhydryl, amine, phosphate, and carboxyl groups, with sulfhydryl having the highest affinity. In its binding with sulfhydryl groups, lead may interfere with the activity of zinc metalloenzymes, as zinc binds to a sulfhydryl group at the active site. Lead also binds to metallothionein, a sulfhydryl-rich protein, but does not appear to displace cadmium or zinc. Metallothionein is induced by cadmium, zinc, and arsenic, but apparently not by lead, although metallothionein sequesters lead in the cell. Another lead-binding protein is an acidic, carboxyl-rich protein found in the kidney and brain (ATSDR 1999b).

Lead interferes with heme synthesis by altering the activity of several mitochondrial and cytosolic enzymes. One of the most sensitive hematological effects is inhibition of the cytosolic enzyme ALAD, with no threshold apparent through the lowest PbB levels (. 3 µg/dL). Lead's inhibition of ALAD occurs

through binding of lead to vicinal sulfhydryls at the active site of ALAD, where zinc is normally bound to a single sulfhydryl. Lead stimulates the mitochondrial enzyme ALAS, through feedback derepression, with a threshold in human leukocytes at a PbB of about 40 µg/dL. As a result of the inhibition of ALAD and stimulation of ALAS, ALA accumulates in blood, urine, and soft tissues. Lead inhibits the insertion of iron into protoporphyrin by the mitochondrial enzyme ferrochelatase, possibly through binding of lead to the sulfhydryl groups of the active site or indirectly through disruption of mitochondrial structure. Inhibition of ferrochelatase results in elevation of zinc protoporphyrin (ZPP) in erythrocytes; ZPP is a sensitive indicator of lead exposure, occurring in children at PbBs of about 25 µg/dL. Effects on heme synthesis are not restricted to the erythrocyte. A number of studies suggest that lead-impaired heme production itself may be a factor in lead's neurotoxicity (ATSDR 1999b).

Mechanisms by which lead might affect blood pressure include effects on several hormonal and neural regulatory systems, changes in vascular smooth muscle reactivity, cardiac muscle contractility, changes in cell membrane cation transport systems, and possible effects on vascular endothelial cells (ATSDR 1999b).

A.4 Health Guidelines

ATSDR (1999b) has not derived MRLs for lead. ATSDR (1999b) has suggested the use of media-specific slope factors and site-specific environmental monitoring data to predict media-specific contributions to blood lead. The predicted contributions from the individual media are summed to yield a total predicted PbB level. The media-specific slope factors were derived from regression analysis of lead concentrations in water, soil, dust, diet, or air and PbBs for various populations.

The CDC determined in 1991 that blood lead levels of >10 µg/dL are to be considered elevated (ATSDR 1999b; CDC 1991).

EPA (IRIS 2001) has not developed a reference concentration (RfC) or RfD for lead. EPA stated that it would be inappropriate to develop an RfD for inorganic lead (and lead compounds) because some of the health effects occur at PbBs so low as to be essentially without a threshold. Instead, EPA defines lead risk as the probability of exceeding a PbB of concern (i.e., 10 µg/dL) in children (EPA 1994a) or in fetuses (EPA 1996). This approach is supported by human epidemiological studies that have associated PbBs exceeding 10 µg/dL with impairment or delays in neurobehavioral development and other effects on children (e.g., blood enzymes). EPA estimates lead risk in children using the IEUBK model (EPA

1994b). This model translates estimates of site-specific exposure concentrations into estimates of the probability that children's blood leads will exceed a PbB of concern.

The National Toxicology Program (NTP 2001) has determined that lead acetate and lead phosphate can reasonably be anticipated to be human carcinogens, based on sufficient evidence of carcinogenicity in experimental animals. NTP (2001) considered lead chromate as one of the "Chromium Hexavalent Compounds." IARC (1987) has determined that the animal data are sufficient to classify lead and some lead compounds as possibly carcinogenic to humans (Group 2B). EPA (IRIS 2001) classified lead in Group B2—probable human carcinogen. EPA did not develop an oral slope factor for lead because of the many uncertainties, some of which may be unique to lead. An EPA inhalation unit risk also is not available for lead (IRIS 2001). ACGIH (1998) classified lead and certain inorganic lead compounds as A3 carcinogens—carcinogenic in animals at relatively high doses not considered relevant to worker exposure. Lead chromate, assessed on the basis of both lead and chromate, was classified by ACGIH (1998) as an A2 carcinogen—carcinogenic in animals at doses considered relevant to worker exposure, but with insufficient epidemiological data to confirm risk to humans.

A.5 Derivation of Target-Organ Toxicity Dose (TTD) Values

TTDs for chronic oral exposure to lead were derived for endpoints affected by lead and one or more of the other chemicals in the lead, arsenic, cadmium, and chromium(VI) mixture that is the subject of this Interaction Profile. The relevant endpoints for this mixture include neurological renal, cardiovascular, hematological, and testicular effects. Chronic oral TTDs for these endpoints are derived below, using the methods described in ATSDR (2001a, Section 2.3.2). Because ATSDR's approach to the assessment of lead uses media-specific slope factors and site-specific contributions to PbB, the TTDs for lead are derived based on PbB as well (see rationale in Chapter 3 of this profile). The derivations are based on data provided in ATSDR (1999b), and particularly Sections 2.2.1 (Effects in Humans Based on Blood Lead (PbB) Levels), 2.5 (Relevance to Public Health), and 2.7 (Biomarkers of Exposure and Effect). The derivation methods used similar reasoning as for the CDC and EPA levels of concern (see neurological effects).

Neurological Effects

A large number of epidemiological studies and case reports indicate that exposure to lead causes neurological effects. Slowing of nerve conduction velocity is associated with PbBs of $\geq 30 \mu\text{g/dL}$ in

children and adults. Of greater concern are the inverse linear relationships between IQ and other neurobehavioral measures in children at PbBs extending down through 10 µg/dL or possibly lower. Children appear to be more sensitive to the neurobehavioral toxicity of lead than are adults. Limited data suggest an association between decreased neurobehavioral performance and PbB in aging subjects at relatively low PbBs, indicating that the elderly may be another sensitive population. Although results of the epidemiological studies in children are not entirely consistent, several meta-analyses have indicated that a highly significant IQ decrement of 1–3 points is associated with a change in PbB from 10 to 20 µg/dL in children (IPCS 1995; Needleman and Gatsonis 1990; Pocock et al. 1994; Schwartz 1994). The CDC (1991) determined that blood lead levels of >10 µg/dL are to be considered elevated in children, based largely on concern for the effects of low-level lead exposure on the central nervous system. EPA defines lead risk as the probability of exceeding a PbB of concern (10 µg/dL) in children or fetuses (EPA 1994a, 1996). The CDC level of concern for lead of 10 µg/dL is adopted as the TTD_{NEURO} .

Renal Effects

Chronic nephropathy is associated with PbB levels of 40–>100 µg/dL in humans exposed to lead occupationally. There are some indications of renal damage in a study in children whose mean PbB was 34.2 µg/dL (increased N-acetyl-β-D-glucosaminidase activity in urine, a sensitive indicator) (Verberk et al. 1996). The value for children, supported by the occupational data, and rounded to 34 µg/dL, is taken as the TTD_{RENAL} .

Cardiovascular Effects

At higher levels of exposure, lead produces cardiac lesions and electrocardiographic abnormalities in humans. Many epidemiological studies have reported an association between increases in blood pressure and increases in PbB. The contribution of lead, as compared with other factors, is relatively small, and whether the associations indicate causality is controversial. Animal data demonstrate that oral exposure to lead increases blood pressure ATSDR (1999b). The correlation between PbB and blood pressure is apparent at relatively low PbBs extending through 10 µg/dL (e.g., Schwartz 1995). Therefore, the CDC level of concern, 10 µg/dL, is adopted as the TTD_{CARDIO} .

Hematological Effects

Lead interferes with the synthesis of heme. The consequence at higher levels of exposure is a hypochromic, normocytic anemia. The most sensitive indicator of effect on heme synthesis is the inhibition of ALAD. ALAD activity is inversely correlated with PbB through the lowest levels of PbB in the general population. Even in the absence of detectable effects on hemoglobin levels, there is concern that effects on heme synthesis may have far-reach impacts, particularly on children (ATSDR 1999b). Accordingly, the CDC PbB of concern, 10 µg/dL (CDC 1991), is selected as the TTD_{HEMATO} .

Testicular Effects

Adverse effects of the testes and sperm have been reported in occupationally exposed men with PbBs of 40–50 µg/dL in some studies, but not in others, and are well-established at higher levels of exposure (PbBs ≥66 µg/dL) (ATSDR 1999b). The point of departure for increased risk of below normal sperm and total sperm count was 40 µg/dL (Alexander et al. 1996). This value is selected as the TTD_{TESTIC} .

Summary (TTDs for Lead)

$TTD_{NEURO} = 10 \text{ µg/dL PbB} = \text{CDC level of concern}$

$TTD_{RENAL} = 34 \text{ µg/dL PbB}$

$TTD_{CARDIO} = 10 \text{ µg/dL PbB}$

$TTD_{HEMATO} = 10 \text{ µg/dL PbB}$

$TTD_{TESTIC} = 40 \text{ µg/dL PbB}$

Appendix B: Background Information for Arsenic

B.1 Toxicokinetics

Arsenic, as soluble arsenate or arsenite, is well-absorbed (~80%) in both humans and animals exposed by the oral route. Judging from the oral toxicity data, arsenic trioxide also is well absorbed. Lower rates of absorption have been observed with insoluble or less soluble forms of arsenic, such as arsenic sulfide and lead arsenate. Absorption appears to occur by passive diffusion. Distribution occurs throughout the body (ATSDR 2000a). Concentrations in skin of humans exposed to background levels of arsenic were higher than in other live tissues except blood (Liebscher and Smith 1968). Arsenic accumulated in the skin of animals following long-term exposure (Lingren et al. 1982). Concentrations in hair and nails tend to be higher than in live tissues. The rat tends to sequester arsenic in erythrocytes. Arsenates (As(V)) and arsenites (As(III)) are interconverted in the body by reduction/oxidation reactions. Reduction of arsenate to arsenite can be mediated by glutathione. Arsenite is methylated to yield the less toxic forms monomethylarsenite (MMA) and dimethylarsenite (DMA). The liver is the major site for the methylation. The methylated forms are excreted primarily in the urine (ATSDR 2000a).

B.2 Health Effects

Chronic oral exposure to arsenic has resulted in serious damage to the vascular system in humans, including Blackfoot disease (a progressive loss of circulation in the fingers and toes that may lead to gangrene), Raynaud's disease, and cyanosis of fingers and toes. The intima of the blood vessels appeared to have thickened. Direct irritation of the gastrointestinal mucosa can occur. Arsenic has caused anemia in humans exposed by the oral route. Increased hemolysis and a toxic effect on the erythropoietic cells of bone marrow may be factors in the development of anemia. Leukopenia has been reported in humans. Hepatic effects seen in humans were thought to be secondary to portal tract fibrosis and portal hypertension, which may have originated from damage to the blood vessels. Signs of renal damage generally are not seen or are mild in humans exposed to arsenic by the oral route. Characteristic dermal lesions caused by long-term oral exposure of humans to arsenic include hyperkeratinization (particularly on the palms and soles), formation of hyperkeratinized corns or warts, and hyperpigmentation of the skin with associated spots of hypopigmentation. A fraction of the hyperkeratinized corns may progress to squamous cell carcinoma of the skin. Signs of peripheral and/or central neuropathy are commonly seen in humans exposed to arsenic orally, with high-dose exposure producing central nervous system effects and low-dose exposure producing peripheral nervous system effects (ATSDR 2000a). The potential for

arsenic to cause subtle neurological effects, such as neurobehavioral effects in children, has not been fully investigated. Studies of associations between hair arsenic concentrations (a biomarker of exposure) and neurobehavioral effects in children have observed an inverse association between hair arsenic and reading and spelling performance (Moon et al. 1985).

Effects on the skin, vascular system and neurological system appear to be relatively sensitive effects of ingested arsenic; dermal effects are the best documented sensitive effect, and the earliest observable sign of health effects from long-term exposure. The NOAEL and LOAEL for dermal effects in humans are 0.0008 and 0.014 mg/kg/day. Hematological effects may be somewhat less sensitive, and renal effects are less sensitive and less common. Epidemiological studies provide convincing evidence that ingestion of arsenic causes cancer of the skin in humans. The lesions include squamous cell carcinomas, which develop from some of the hyperkeratotic arts or corns, and multiple basal cell carcinomas, arising from cells not associated with hyperkeratinization. Evidence is mounting that ingested arsenic may increase the risks of internal cancers as well (ATSDR 2000a).

Some of the effects of arsenic seen in humans are supported by the animal data, but animals do not develop dermal lesions and cancer as a result of oral arsenic exposure. Changes in vascular reactivity have been reported in rats given repeated oral arsenic doses of 11 mg/kg/day (ATSDR 2000a). Hematological and hematopoietic effects, including decreased hematocrit and increased urinary excretion of porphyrins, have been observed in intermediate-duration dietary studies of arsenic in rats at doses of 2.5 mg/kg/day (Fowler and Mahaffey 1978; Mahaffey et al. 1981), and in chronic oral studies in dogs at 2.4 mg/kg/day (ATSDR 2000a). Intermediate oral studies in rats demonstrated alterations in renal mitochondria at 2.5 and 4.7 mg/kg/day (ATSDR 2000a; Mahaffey and Fowler 1977; Mahaffey et al. 1981). Mild proteinuria was observed rats following a single oral dose of 10 mg/kg/day (ATSDR 2000a). Oral administration of arsenic to mice at 8 mg/kg/day altered neurotransmitter concentrations in some areas of the brain (Mejia et al. 1997). Developmental effects have been seen following high oral doses of arsenic in animals, but these are not sensitive effects (ATSDR 2000a).

B.3 Mechanisms of Action

At relatively high oral exposure, methylation capacity may not be adequate to prevent cytotoxic levels of arsenic(III) from reaching tissues. Some of the effects of higher-dose oral exposure to arsenic are thought to be the result of direct cytotoxicity; these include gastrointestinal irritation, and dermal and neurological effects (ATSDR 2000a). Arsenic(III) reacts with the sulfhydryl groups of proteins, inactivates enzymes,

and interferes with mitochondrial function by inhibiting succinic dehydrogenase activity and uncoupling oxidative phosphorylation. It has been proposed that arsenic may compete with phosphate during oxidative phosphorylation and may inhibit energy-linked reduction of nicotinamide adenine dinucleotide (NAD) (Goyer 1995). Chronic low-level exposure to arsenic is thought to stimulate keratinocyte secretion of growth factors the resulting increase in cell division and DNA replication affords greater opportunities for genetic damage. Arsenic induces metallothionein, a metal-binding protein. Only a small percentage of administered arsenic is bound to metallothionein, and the affinity of arsenic for metallothionein is much lower than that of cadmium or zinc (ATSDR 2000a). It has been suggested that metallothionein may protect against arsenic toxicity by acting as an antioxidant against oxidative injury produced by arsenic (ATSDR 2000a; NRC 1999).

B.4 Health Guidelines

ATSDR (2000a) did not derive inhalation MRLs or an intermediate oral MRL for arsenic due to lack of suitable studies.

ATSDR (2000a) derived a provisional acute oral MRL of 0.005 mg/kg/day for arsenic based on a LOAEL of 0.05 mg/kg/day for facial (periorbital) edema and gastrointestinal irritation in poisoning cases from arsenic-contaminated soy sauce in Japan (Mizuta et al. 1956). These effects were the initial effects, and in some patients, were followed by dermal lesions, neuropathy (hypesthesia in legs, abnormal patellar reflex), mild anemia, mild degenerative liver lesions and hepatic dysfunction, and abnormal electrocardiogram. An uncertainty factor of 10 was applied to account for the use of a LOAEL. The MRL is considered provisional because the gastrointestinal effects were serious and because serious neurological and cardiovascular effects also occurred at the same dose.

ATSDR (2000a) derived a chronic oral MRL of 0.0003 mg/kg/day for arsenic based on a NOAEL of 0.0008 mg/kg/day for dermal lesions in male and female farmers exposed to high levels of arsenic in well water in Taiwan. An uncertainty factor of 3 was applied to account for human variability.

EPA has not derived an RfC for arsenic (IRIS 2001).

EPA (IRIS 2001) derived a chronic RfD of 0.0003 mg/kg/day for arsenic based on a NOAEL of 0.0008 mg/kg/day for dermal lesions and possible vascular complications for farmers in Taiwan, which also was used as the basis for the ATSDR chronic oral MRL. An uncertainty factor of 3 was applied to

account for the lack of reproductive data and to account for some uncertainty in which the NOAEL in the critical study accounts for all potentially sensitive individuals.

The National Toxicology Program (NTP 2001) has determined that inorganic arsenic compounds are known to be human carcinogens, based on sufficient evidence of carcinogenicity in humans. The International Agency for Research on Cancer (IARC 1987) concluded that there is sufficient evidence of a relationship between exposure to arsenic and human cancer, and classifies arsenic in Group 1. The American Conference of Governmental Industrial Hygienists (ACGIH) classifies arsenic (elemental and inorganic compound) as a confirmed human carcinogen; cancer category A1 (ACGIH 1998). EPA (IRIS 2001) has classified arsenic in Group A—Human carcinogen, based on increased lung cancer mortality in several human populations exposed primarily through inhalation, increased mortality from internal organ cancers (liver, kidney, lung, and bladder), and increased incidences of skin cancer in populations exposed to arsenic through drinking water. An oral slope factor of 1.5 per (mg/kg)/day was derived based on analysis of the skin cancer data from a Taiwanese population exposed through drinking water. An inhalation unit risk of 4.3×10^{-3} per $\mu\text{g}/\text{m}^3$ was derived based on age-specific mortality from lung cancer in male smelter workers.

B.5 Derivation of Target Organ Toxicity Dose (TTD) Values

TTDs for oral exposure to arsenic were derived for endpoints affected by arsenic and one or more of the other chemicals in the lead, arsenic, cadmium, and chromium mixture that is the subject of this Interaction Profile. The relevant endpoints for this mixture include neurological, renal, cardiovascular, hematological, and testicular effects. Chronic oral TTDs for these endpoints are derived below, using the methods described by ATSDR (2001a, Section 2.3.2). The derivations are based on data provided in ATSDR (2000a), and in particular, the oral LSE table. Where the data are inadequate to derive a chronic oral TTD for a given endpoint, the chronic oral MRL is recommended as a conservative alternative that is protective of human health.

Neurological Effects

A large number of epidemiology studies and case reports indicate that ingestion of arsenic can cause injury to the nervous system. A symmetrical peripheral neuropathy has been observed in individuals exposed to 0.004–0.5 mg As/kg/day for an intermediate or chronic duration (ATSDR 2000a). The neuropathy is characterized by numbness in the hands and feet progressing to a painful pins and needles

sensation and dying-back axonopathy with demyelination. Additionally, a significant association between decreased reading and spelling performance and hair arsenic levels was found in a group of elementary school children (Moon et al. 1985), suggesting that arsenic may also cause neurobehavioral effects. A TTD_{NEURO} can be derived using a study by Lianfang and Jianzhong (1994) of approximately 31,000 residents living in areas of China with high arsenic levels in the drinking water. This study identified NOAEL and LOAEL values of 0.003 and 0.004 mg As/kg/day, respectively, for an increased occurrence of numbness of the extremities. Dividing the NOAEL by an uncertainty factor of 10 for intrahuman variability results in a TTD_{NEURO} of 0.0003 mg As/kg/day.

Renal Effects

Although there have been some reports of kidney injury in humans ingesting arsenic, most studies did not report clinical signs of significant renal injury (ATSDR 2000a). When renal effects were observed they were often secondary to fluid imbalances or vascular injury. Several animal studies have reported renal effects following intermediate- or chronic-duration oral exposure. The effects include increased kidney weight, swollen mitochondria and increased numbers of dense autophagic lysosome-like bodies in the proximal tubules, increased pigmentation in the proximal tubules, and cysts (ATSDR 2000a). The ultrastructural changes in the proximal tubules were observed at 4.7 mg As/kg/day (Brown et al. 1976), which is the lowest identified LOAEL for renal effects in animal studies. However, the toxicological significance of this effect is not known. The next highest LOAEL is 20 mg As/kg/day identified in rats exposed to arsenic in the feed for 2 years (Byron et al. 1967). At 20 mg/kg/day and higher there was an increase in pigmentation in the proximal tubules and increased number of cysts in the renal cortex; no effects were observed at 9 mg As/kg/day. The Byron et al. (1967) study was selected as the basis of the TTD_{RENAL} . The NOAEL of 9 mg As/kg/day was divided by an uncertainty factor of 100 (10 for interspecies differences and 10 for intrahuman variability) to derive a TTD_{RENAL} of 0.09 mg As/kg/day.

Cardiovascular Effects

The cardiovascular system is a very sensitive target of arsenic toxicity. A number of effects have been observed including heart damage (myocardial depolarization, hypertrophy of the ventricular wall, cardiac arrhythmias), vascular damage (Raynaud's disease, Blackfoot disease, arterial thickening), and hypertension (ATSDR 2000a). The series of studies by Tseng and associates (Tseng 1977; Tseng et al. 1968, 1995, 1996) provide suggestive evidence that Blackfoot disease and dermal hyperkeratosis and hyperpigmentation would occur at similar dose levels. Thus, the chronic-duration oral MRL of

0.0003 mg As/kg/day (based on the dermal effects reported by Tseng [1977] study) can also be used as the TTD_{CARDIO} .

Hematological Effects

Numerous studies have reported anemia in humans and animals ingesting arsenic (ATSDR 2000a). The available human studies reported significant increases in the occurrence of anemia at doses of 0.05 mg As/kg/day and higher (Franzblau and Lilis 1989; Wagner et al. 1979; Zaldivar and Guillier 1977). In a study of Utah residents with elevated levels of arsenic in the drinking water for at least 5 years, the incidence of anemia was not significantly higher than control populations (Southwick et al. 1981). This NOAEL of 0.006 mg As/kg/day and an uncertainty factor of 10 for intrahuman variability was used to derive a TTD_{HEMATO} of 0.0006 mg As/kg/day.

Testicular Effects

There is limited information on the potential reproductive toxicity of arsenic. In a 3-generation reproductive toxicity study, no alterations in reproductive success were observed at 1.2 mg As/kg/day (Schroeder and Mitchner 1971). Another study found an 8% decrease in testes weight in mice exposed to 0.0085 mg As/kg/day in drinking water for 32 days; no functional tests were conducted (Healy et al. 1998). Thus, the available data are inadequate to determine whether the testes are a target of concern for arsenic and a TTD_{TESTIC} was not derived.

Summary (TTDs for Arsenic)

$TTD_{\text{NEURO}} = 0.0003 \text{ mg As/kg/day } (3 \times 10^{-4} \text{ mg/kg/day})$

$TTD_{\text{RENAL}} = 0.09 \text{ mg As/kg/day } (9 \times 10^{-2} \text{ mg/kg/day})$

$TTD_{\text{CARDIO}} = 0.0003 \text{ mg As/kg/day } (3 \times 10^{-4} \text{ mg/kg/day})$

$TTD_{\text{HEMATO}} = 0.0006 \text{ mg As/kg/day } (6 \times 10^{-4} \text{ mg/kg/day})$

$TTD_{\text{TESTIC}} = \text{Not applicable}$

Appendix C: Background Information for Cadmium

C.1 Toxicokinetics

Ingested cadmium is poorly absorbed. Approximately 5% of the total cadmium ingested in food or water is absorbed. Cadmium absorption increases with iron or calcium deficiency. Absorption from the gut appears to take place in two phases—uptake from the lumen into the mucosa, and transfer from the mucosa into the circulation. Cadmium is distributed throughout the body, but the major portion is found in the liver and kidney. The majority of absorbed cadmium is retained in the tissues. Half-times for cadmium in the human kidney have been estimated at 6–38 years, and in human liver at 4–19 years. Cadmium concentrations in the kidney are near zero at birth, but rise with age to a peak (generally around 40–50 µg Cd/g wet weight) between ages 50 and 60, after which renal concentrations plateau or decline. Hepatic concentrations of cadmium also are near zero at birth, increasing to values of 1–2 µg/g wet weight by age 20–25, and increase only slightly thereafter. Thus, renal concentrations far exceed hepatic concentrations following prolonged exposure. Cadmium does not undergo metabolic conversion, but the cadmium ion can readily bind to anionic groups, especially sulfhydryl groups, in proteins and other molecules. Cadmium is bound to the protein metallothionein in the liver, which releases the metallothionein-cadmium complex, rather than free cadmium, into the bloodstream. Metallothionein is a low-molecular-weight, sulfhydryl-rich protein that normally binds zinc. Metallothionein-bound cadmium is readily filtered by the renal glomerulus and reabsorbed from the glomerular filtrate by the proximal tubule cells, at which point the “exogenous” metallothionein is catabolized in tubular lysosomes, releasing free cadmium. The free cadmium stimulates the synthesis of metallothionein in the tubular cells, is then bound to the tubular metallothionein, and remains in the cells. Most of the ingested cadmium is excreted unabsorbed in the feces. Most of the absorbed cadmium is retained; some excretion of cadmium occurs through the urine, and urinary excretion increases with renal damage (ATSDR 1999a).

C.2 Health Effects

Cadmium is considered a cumulative toxicant. The human exposure scenarios of greatest concern are long-term oral exposures. Cadmium accumulates in the kidney over a period of approximately 50 years; renal damage appears to be a consequence of this accumulation, such that the ability of the kidney to sequester cadmium through synthesis of metallothionein may be overwhelmed. Renal effects have been seen in humans and animals by both inhalation and oral exposure, and are the most sensitive effects of chronic oral exposure, occurring at intakes as low as 0.0078 mg/kg/day. Effects of cadmium other than

renal damage are not considered by ATSDR (1999a) to be sensitive effects. Nevertheless, some effects that are seen at moderately low levels of oral exposure are cardiovascular, hematological, neurological, and testicular effects. Cardiovascular effects (hypertension) have been reported in humans and animals in some studies and not in others. ATSDR (1999a) has concluded that the magnitude of any effect of cadmium on blood pressure is small compared with other determinants of hypertension, and that cardiovascular effects are not a sensitive endpoint for cadmium. Oral exposure to cadmium can cause anemia in humans and animals, but is not considered by ATSDR (1999a) to be likely to result from low level exposure. Hepatic effects occur with higher oral doses of cadmium, usually for acute or intermediate durations. A few studies have reported associations between environmental cadmium exposure (using hair cadmium as a biomarker) and neurobehavior effects including verbal IQ in children and disruptive behavior in young adults. Neurological effects have been seen in animals exposed to cadmium orally, and include changes in behavior, including a decrease in motor activity, alterations in neurotransmitter levels, histopathological changes in the brain, and peripheral neuropathy. These effects occurred in animals at doses as low as 1.4 mg/kg/day. Testicular effects have been seen from oral dose ranges of 5–14 mg/kg/day in animal studies. Although inhalation exposure to cadmium appears to be carcinogenic, oral exposure does not (ATSDR 1999a).

C.3 Mechanisms of Action

Cadmium is a cumulative renal toxicant. Cadmium accumulates in the kidney over the lifetime; toxicity is thought to result when a critical concentration of cadmium is reached in the kidney. Much of the cadmium in the kidney and in other tissues is bound to metallothionein, which is thought to sequester cadmium, preventing damage to cellular constituents, but which also retains cadmium in the cell. Metallothionein is thought to function in the storage of the essential metals zinc and copper, and to serve as an antioxidant. Details regarding the mechanism of cadmium renal toxicity are uncertain; renal damage is hypothesized to occur when an excessive concentration of free cadmium occurs intracellularly in the kidney, perhaps due to an insufficient rate of renal metallothionein synthesis to bind the intrarenal cadmium. The free cadmium may bind to other intracellular ligands, including metalloenzymes, and may destabilize proximal tubule cell membranes (ATSDR 1999a; IRIS 2001). Whether the accumulation of the CdMT complex devotes disproportionate cellular resources to sequestration of cadmium and may contribute to toxicity through lack of metallothionein for other needs does not appear to have been considered as a possible mechanism.

Although intracellular renal metallothionein protects against the toxicity of cadmium, when released from the liver or administered by injection, CdMT is directly and indirectly toxic to the kidney. The CdMT that reaches the kidney through the circulation is filtered by the glomerulus, is directly toxic to the brush border membrane of the proximal convoluted tubules (Cherian 1985; Suzuki and Cherian 1987), and, following reabsorption by the proximal convoluted tubules, is indirectly toxic through degradation of the metallothionein and release of free cadmium intracellularly, which may cause tissue damage unless the capacity of the kidney to produce intracellular metallothionein to bind the cadmium is sufficient (ATSDR 1999a).

MT-null mice (mice that lack the ability to synthesize MT) are unusually susceptible to the renal, hepato-, immuno-, and hematotoxicity and to the lethality of subcutaneously injected cadmium (Habeebu et al. 2000; Liu et al. 1998, 1999a). MT-null mice also are unusually susceptible to the renal toxicity of subcutaneously injected CdMT (Liu et al. 1999b). These findings indicate the importance of intracellular MT in protecting against multi-organ cadmium toxicity, and that the toxicity of cadmium to the kidney is not mediated solely through CdMT. Single-dose oral studies in normal and MT-1 transgenic mice (which carry extra copies of a MT gene and have higher constitutive levels of MT in their tissues, particularly in the liver) indicate that at a relatively high dose of cadmium (300 $\mu\text{mole/kg}$ [34 mg/kg], close to the maximum tolerated dose), cadmium retention in the whole body, liver, and kidney 1 week after dosing are approximately double those seen in normal mice, and (induced) metallothionein levels are approximately triple the levels in normal mice. At lower doses of cadmium, differential retention generally did not occur, even though levels of MT were higher in the MT-1 transgenic mice than in the normal mice. Levels of MT in the intestine are also higher in the MT-1 transgenic mice, but did not appear to impair absorption of cadmium. The relevance of these results to intermediate or chronic exposure is uncertain. Predicting the consequences of concurrent oral exposure to metallothionein-inducers and cadmium is problematic because the outcome would depend on the balance between release of the toxic CdMT complex from liver versus induction of renal intracellular MT to bind (detoxify) cadmium. In addition, retention of cadmium in the kidney (and other tissues) is associated with binding of cadmium to intracellular MT. When the concentration of cadmium in the kidney reaches a critical concentration, renal dysfunction ensues (ATSDR 1999a; IRIS 2001). Therefore, MT induction may provide some short-term protection against renal damage, but could conceivably contribute to an increased accumulation of cadmium in the kidney and the subsequent development of chronic renal toxicity.

Cadmium is known to alter neurotransmitter levels in the brain, and may inhibit calcium entry into neurons (ATSDR 1999a; Nation et al. 1989). Testicular effects of cadmium may be due to cadmium

interference with zinc-protein complexes that control DNA transcription, subsequently leading to apoptosis (ATSDR 1999a).

C.4 Health Guidelines

ATSDR (1999a) did not derive inhalation MRLs or acute or intermediate oral MRLs for cadmium due to lack of suitable studies.

ATSDR (1999a) derived a chronic oral MRL of 0.0002 mg/kg/day for cadmium based on a NOAEL for β_2 -microglobulinuria (an indicator of renal damage) of 0.0021 mg/kg/day in humans, corresponding to a total lifetime cadmium intake of 2,000 mg. An uncertainty factor of 10 was applied to the NOAEL to account for human variability.

EPA has not derived an RfC for cadmium (IRIS 2001).

EPA derived chronic RfDs of 0.0005 mg/g/day for water and 0.001 mg/kg/day for food for cadmium, based on NOAELs of 0.005 mg/kg/day for water and 0.01 mg/kg/day for food (IRIS 2001). The NOAELs were estimated with a toxicokinetic model from a human NOAEL of 200 $\mu\text{g Cd/g}$ wet renal cortex for proteinuria (an indicator of renal damage). The different values for food and water reflect EPA opinion regarding bioavailability from these media.

The National Toxicology Program (NTP 2001) has classified cadmium and cadmium compounds as known to be human carcinogens, based on sufficient evidence of carcinogenicity from studies in humans. IARC (1993) concluded that cadmium and cadmium compounds are carcinogenic to humans (Group 1). EPA (IRIS 2001) classified cadmium in Group B1—probable human carcinogen, and derived an inhalation unit risk of 1.8×10^{-3} per $\mu\text{g/m}^3$ for cadmium based on lung, trachea, and bronchus cancer mortality in male workers in a cadmium smelter. EPA (IRIS 2001) noted that seven oral studies of cadmium salts in rats and mice have given no evidence of carcinogenicity, and that studies of ingestion in humans are inadequate to assess carcinogenicity.

C.5 Derivation of Target Organ Toxicity Dose (TTD) Values

TTDs for oral exposure to cadmium were derived for endpoints affected by cadmium and one or more of the other chemicals in the lead, arsenic, cadmium, and chromium mixture that is the subject of this Interaction Profile. The relevant endpoints for this mixture include neurological, renal, cardiovascular, hematological, and testicular effects. Chronic oral TTDs for these endpoints are derived below, using the methods described by ATSDR (2001a, Section 2.3.2). The derivations are based on data provided in ATSDR (1999a), and in particular, the oral LSE table. Where the data are inadequate to derive a chronic oral TTD for a given endpoint, the chronic oral MRL for cadmium is recommended as a conservative alternative that is protective of human health.

Neurological Effects

Neurological effects consisting of decreased motor activity, weakness and muscle atrophy, aggressive behavior, increased passive avoidance, and alterations in brain dopamine, 5-hydroxytryptamine, succinic dehydrogenase, and monoamine oxidase levels have been observed in rats exposed to 3.1–24 mg Cd/kg/day for an intermediate duration (ATSDR 1999a). In mice, necrosis of the choroid plexus epithelial cells have been observed following intermediate duration exposure to 1.4 mg Cd/kg/day as cadmium chloride in drinking water, but not after exposure to 0.2 mg Cd/kg/day (Valois and Webster 1989). Chronic exposure to 3.6 mg Cd/kg/day as cadmium chloride in drinking water resulted in peripheral neuropathy in rats (Sato et al. 1978). The lowest LOAEL for neurological effects was identified in the intermediate duration mouse study; this study was selected as the basis of the TTD_{NEURO} . A TTD_{NEURO} of 0.0002 mg Cd/kg/day was calculated by dividing the NOAEL of 0.2 mg Cd/kg/day identified in the Valois and Webster (1989) study by an uncertainty factor of 1,000 (10 for use of an intermediate-duration study, 10 for interspecies differences and 10 for intrahuman variability)

Renal Effects

Numerous human and animal studies indicate that the kidney is the main target of cadmium toxicity (ATSDR 1999a). The kidney damage is characterized as decreased reabsorption of filtered low molecular weight proteins and mild tubular lesions progressing to necrosis. The chronic oral MRL for cadmium of 0.0002 mg Cd/kg/day is based on renal effects.

Cardiovascular Effects

A number of human and animal studies have found a relationship between ingestion of cadmium and increased blood pressure, but other studies have not found any significant association (ATSDR 1999a). ATSDR (1999a) concluded that the evidence for cardiovascular toxicity resulting from oral exposure to cadmium is suggestive of a slight effect and that the magnitude of any effect of cadmium on blood pressure is small compared with other determinants of hypertension. Increases in blood pressure have been observed in animals exposed to doses of 0.0081–1.6 mg Cd/kg/day and 0.01–1.71 mg Cd/kg/day following intermediate or chronic exposure, respectively. The Perry et al. (1989) and Kopp et al. (1982) studies identified the lowest LOAELs for hypertension following intermediate- and chronic-duration exposure, respectively; however, these studies were not selected as the basis of the TTD_{CARDIO} because of the uncertainty regarding the relevance to human exposures of the very low metal diet and environment used in the animal studies. (See “Animal Studies—Oral Exposure” in Section 2.2.4 for further discussion of the studies by this group of investigators.) Thus, the Akahori et al. (1994) chronic monkey study was selected as the basis of the TTD_{CARDIO} . This study identified NOAEL and LOAEL values of 0.53 and 1.71 mg Cd/kg/day, respectively, for increases in blood pressure in Rhesus monkeys exposed to cadmium chloride in the diet for 9 years; blood pressure effects were only observed during the first 1.5 years. Dividing this NOAEL by an uncertainty factor of 100 (10 for interspecies differences and 10 for intrahuman variability) results in a TTD_{CARDIO} of 0.005 mg Cd/kg/day.

Hematological Effects

Oral cadmium exposure reduces gastrointestinal uptake of iron, which can result in anemia if dietary intake of iron is low. In animal studies, administration of additional iron prevents the anemia. Anemia has been observed in some human oral studies and in a number of animal oral studies of cadmium. Following intermediate-duration exposure, anemia has been observed in rats, mice, and rabbits exposed to doses of 0.8 mg Cd/kg/day and higher (ATSDR 1999a). In chronic-duration studies, anemia was observed in monkeys exposed to 4.0 mg Cd/kg/day. Although a human study (Shiwen et al. 1990) identified a NOAEL of 0.0078 mg Cd/kg/day for anemia in individuals exposed to cadmium for at least 25 years, this study was not selected as the basis of a TTD_{HEMATO} because both the control and exposed populations had very high incidences of anemia (65–73%), which are much higher than in the U.S. population. Additionally, the monkey study was not selected as the basis of the TTD because an intermediate-duration study identified a lower LOAEL. The TTD_{HEMATO} is based on the LOAEL of 0.8 mg Cd/kg/day identified in rats exposed to cadmium chloride in drinking water for 4 weeks (Ogoshi

et al. 1989); a NOAEL was not identified in this study. The NOAEL is divided by an uncertainty factor of 1,000 (10 for use of a LOAEL, 10 for interspecies differences, and 10 for intrahuman variability) resulting in a TTD_{HEMATO} of 0.0008 mg Cd/kg/day. Because the hematological effects are secondary to decreased iron intake rather than a direct effect of cadmium on the hematological system, it is not likely that the effect is duration-related, thus, an uncertainty factor was not used to account for the use of an intermediate-duration study.

Testicular Effects

Testicular effects have been observed in animals exposed to cadmium for acute or intermediate durations; the testicular effects included necrosis and atrophy of seminiferous tubule epithelium, increased testes weight, and decreased sperm count and motility (ATSDR 1999a). Chronic oral studies have not tested the reproductive toxicity of cadmium. The oral studies suggest that the testicular effects occur at doses of 5.8 mg Cd/kg/day and higher. NOAEL and LOAEL values of 2.9 and 5.8 mg Cd/kg/day, respectively, for increased relative testes weight were identified in a study in which rats were exposed to cadmium chloride in the drinking water for 14 weeks (Pleasants et al. 1992). TTD_{TESTIC} of 0.003 mg Cd/kg/day is based on this NOAEL and an uncertainty factor of 1,000 (10 for use of an intermediate-duration study, 10 for interspecies differences, and 10 for intrahuman variability).

Summary (TTDs for Cadmium)

$TTD_{NEURO} = 0.0002 \text{ mg Cd/kg/day } (2 \times 10^{-4} \text{ mg/kg/day})$

$MRL_{(RENAL)} = 0.0002 \text{ mg Cd/kg/day } (2 \times 10^{-4} \text{ mg/kg/day})$

$TTD_{CARDIO} = 0.005 \text{ mg Cd/kg/day } (5 \times 10^{-3} \text{ mg/kg/day})$

$TTD_{HEMATO} = 0.0008 \text{ mg Cd/kg/day } (8 \times 10^{-4} \text{ mg/kg/day})$

$TTD_{TESTIC} = 0.003 \text{ mg Cd/kg/day } (3 \times 10^{-3} \text{ mg/kg/day})$

Appendix D: Background Information for Chromium(VI)

D.1 Toxicokinetics

The absorption of chromium(VI) through the gastrointestinal tract after oral exposure of humans is about 2–10% for potassium chromate. The chromate anion can enter cells by facilitated diffusion through nonspecific anion channels, similarly to phosphate and sulfate anions. Absorption efficiency appears to increase with increasing dose. Once in the blood, chromium is distributed to all organs of the body; preferential distribution to any particular organ does not appear to occur. Chromium(VI) does not appear to accumulate in the body. Chromium(VI) is unstable in body fluids and tissues, including the gastric juice, and is reduced to chromium(V), chromium(IV), and ultimately to chromium(III) by many substances, including ascorbate and glutathione. Absorbed chromium is excreted primarily in the urine; the half-time for excretion of chromium following administration of potassium chromate in drinking water was estimated at 35–40 hours in humans. Minor pathways of excretion are through the hair and nails. Much of the chromium from ingested chromium(VI) passes through the body without being absorbed and is excreted in the feces (ATSDR 2000b).

D.2 Health Effects

Accidental or intentional ingestion of very high doses of chromium(VI) compounds has resulted in severe respiratory, cardiovascular, gastrointestinal, hematological, hepatic, renal, and neurological effects. Respiratory and cardiovascular effects are not generally seen at nonlethal doses. Gastrointestinal effects are associated with irritating effects on the mucosa at high concentrations of chromium(VI). Hematological effects (reduced MCV and MCH) have been seen in rats and mice fed chromium(VI) in the diet for intermediate durations, with a LOAEL of approximately 8 mg/kg/day in rats and 32 mg Cr(VI)/kg/day in mice. Renal effects included accumulation of lipids and inhibition of membrane enzymes in rats given chromium(VI) at 13.5 mg/kg/day by gavage, and proteinuria in rats given chromium(VI) at 98 mg/kg/day from drinking water. An exacerbation of chromium contact dermatitis has been seen in chromium(VI)-sensitized individuals given an oral dose of chromium(VI). In a single study in rats, chromium(VI) produced increased proliferative responses to T- and B-lymphocytes to mitogens, effects consistent with sensitization. Decreased motor activity and balance were seen in rats given 98 mg/kg/day of chromium (VI) in drinking water for 28 days. Testicular effects occurred in rats given 40 mg/kg/day for 90 days, and altered male sexual behavior has been noted at a similar dose. Chromium(VI) administration to rats and mice during gestation by the oral route was developmentally

toxic at 51 mg/kg/day. Although chromium(VI) is a human carcinogen by the inhalation route of exposure, there is no evidence that it is carcinogenic by the oral route (ATSDR 2000b).

D.3 Mechanisms of Action

As previously mentioned, chromium(VI) enters the cells through membrane channels that also admit sulfate and phosphate. Once in the cell chromium(VI) is reduced to chromium(III), with chromium(V) and (IV) as intermediates. The reactions commonly involve intracellular species such as ascorbate, glutathione, or amino acids. Chromium(VI), (V), and (IV) have been shown to be involved in oxidative cycling, generating oxygen radical species. The formation of these radicals may be responsible for many of the deleterious effects of chromium on cells, which can be blocked by radical scavengers. This mechanism appears to have been explored in terms of their potential impact on the induction of carcinogenic responses, and the data appear to have been obtained primarily *in vitro*. *In vivo* studies, however, reported that the antioxidant ascorbate protected against the lethality of dermally administered chromium(VI) and the nephrotoxicity of subcutaneously injected chromium(VI), through reduction of chromium(VI) to chromium(III) (ATSDR 2000b). Once formed from reduction of chromium(VI) within the cell, chromium(III) is thought to complex with intracellular macromolecules (Goyer 1995). It may bind to proteins through a variety of functional groups (de Meester and Hodgson 1977; de Meester et al. 1977).

D.4 Health Guidelines

ATSDR (2000b) derived an inhalation MRL of 0.000005 mg Cr(VI)/m³ (as chromic acid [chromium trioxide mist] and other dissolved chromium(VI) aerosols and mists) for intermediate-duration exposure. The MRL was based on a LOAEL of 0.002 mg Cr(VI)/m³ for nasal lesions in workers. To derive the MRL, the LOAEL was adjusted for continuous exposure (0.0005 mg Cr(VI)/m³) and divided by an uncertainty factor of 100 (10 for human variability and 10 for extrapolating from a LOAEL). ATSDR also derived an MRL of 0.001 mg Cr(VI)/m³ for intermediate exposure to particulate chromium(VI) compounds, based on a benchmark concentration (BMC) of 0.016 mg/m³ for increased levels of lactate dehydrogenase in bronchoalveolar lavage fluid in rats. The BMC was converted to a BMC_{ADJ} and divided by an uncertainty factor of 30 (3 for pharmacodynamic differences not addressed by the dose conversion and 10 for human variability).

ATSDR (2000b) did not derive oral MRLs for chromium(VI) (or chromium(III)) because of insufficient to conflicting data on reproductive and developmental effects. Instead, the upper end of the range of the estimated safe and adequate daily dietary intake of 200 µg Cr/kg/day (NRC 1989) was adopted as provisional guidance for oral exposure to chromium(VI) and chromium(III).

The NRC (1989) derived its estimated safe and adequate daily dietary intakes for (trivalent) chromium of 50–200 µg/day for adults, based on data regarding chromium intake from typical Western diets, the beneficial effect of chromium supplementation in the United States on subjects with impaired glucose tolerance, and the low toxicity of trivalent chromium. The NRC further stated that because humans cannot oxidize the nontoxic trivalent food chromium to the potentially carcinogenic hexavalent chromate compounds, the carcinogenicity of certain chromates is not relevant to the nutritional role of the trivalent form.

EPA (IRIS 2001) derived a chronic inhalation RfC of 0.008 µg Cr(VI)/m³ for chromic acid mists and dissolved chromium(VI) aerosols, based on a LOAEL for nasal septum atrophy in workers exposed to 0.002 mg Cr(VI)/m³. An uncertainty factor of 90 (3 for extrapolation from subchronic to chronic, 3 for extrapolation from a LOAEL to NOAEL, and 10 for human variation) was applied to a LOAEL_{ADJ}.

EPA (IRIS 2001) also derived a chronic inhalation RfC of 0.0001 mg Cr(VI)/m³ for chromium(VI) particulates, based on a benchmark concentration of 0.016 mg Cr(VI)/m³ derived from data for lactate dehydrogenase activity in bronchoalveolar lavage fluid in rats.

EPA (IRIS 2001) derived a chronic oral reference dose (RfD) of 0.003 mg Cr(VI)/kg/day for soluble salts of chromium(VI) (e.g., potassium chromate, sodium chromate, potassium dichromate, and sodium dichromate), based on a NOAEL of 2.5 mg Cr(VI)/kg/day for systemic effects in rats exposed to potassium chromate in the drinking water for 1 year.

NTP (2001) lists certain chromium(VI) compounds as substances that are known to be human carcinogens, based on sufficient evidence of carcinogenicity in humans. This classification is based on sufficient evidence for calcium chromate, chromium trioxide, lead chromate, strontium chromate, and zinc chromate. IARC (1990) classifies chromium(VI) in Group 1, carcinogenic to humans, based on sufficient evidence in humans for the carcinogenicity of chromium(VI) compounds as encountered in the chromate production, chromate pigment production, and chromium plating industries; sufficient evidence in experimental animals for the carcinogenicity of calcium chromate, zinc chromates, strontium chromate,

and lead chromates; limited evidence in experimental animals for the carcinogenicity of chromium trioxide and sodium dichromate; and data that support the concept that chromium(VI) ions generated at critical sites in the target cells are responsible for the carcinogenic action observed. EPA has classified chromium(VI) in Group A, a known human carcinogen by the inhalation route of exposure. For the oral route, chromium(VI) is classified as Group D, not classified as to human carcinogenicity (IRIS 2001).

D.5 Derivation of Target Organ Toxicity Dose (TTD) Values

TTDs for oral exposure to chromium(VI) were derived for endpoints affected by chromium(VI) and one or more of the other chemicals in the lead, arsenic, cadmium, and chromium mixture that is the subject of this Interaction Profile. The relevant endpoints for this mixture include neurological, renal, cardiovascular, hematological, and testicular effects. Chronic oral TTDs for these endpoints are derived below, using the methods described by ATSDR (2001a, Section 2.3.2). The derivations are based on data provided in ATSDR (2000b), and in particular, the oral LSE table. Where the data are inadequate to derive a chronic oral TTD for a given endpoint, the RfD for chromium(VI) is recommended as a conservative alternative that is protective of human health.

Neurological Effects

There is limited information on the neurotoxicity of chromium(VI). Dizziness, headache, and weakness were reported by workers exposed to high concentrations of chromium(VI) oxide (chromium trioxide) (Lieberman 1941). In rats, decreased motor activity and ponderal balance were observed following a 28-day exposure to 100 mg Cr(VI)/kg/day as sodium chromate in drinking water (Diaz-Mayans et al. 1986); no effects were observed at 10 mg Cr(VI)/kg/day. A decrease in motor activity was observed in rats following intraperitoneal administration of sodium chromate (Diaz-Mayans et al. 1986). The NOAEL identified in the Diaz-Mayans et al. (1986) drinking water study is a suitable basis for a TTD. Application of an uncertainty factor of 1,000 (10 for extrapolation from rats to humans, 10 for intrahuman variability, and 10 to extrapolate from an intermediate-duration study) to the NOAEL results in a TTD_{NEURO} of 0.01 mg Cr(VI)/kg/day.

Renal Effects

Severe renal impairment, renal failure, and necrosis of the renal tubules have been reported in cases of fatal or near fatal ingestion of chromium(VI) and impaired renal function has been reported in workers

exposed to airborne chromium(VI) (ATSDR 2000b). Renal effects have also been reported in experimental animal studies. An accumulation of lipids and inhibition of membrane enzymes were observed in rats administered via gavage 13.5 mg Cr(VI)/kg/day as potassium chromate for 20 days (Kumar and Rana 1982, 1984) and oliguria and proteinuria were observed in rats receiving 100 mg Cr(VI)/kg/day as sodium chromate in drinking water for 28 days (Diaz-Mayans et al. 1986). In a series of studies conducted by NTP, no histological alterations were observed in rats or mice exposed to doses as high as 9.8 or 48 mg Cr(VI)/kg/day, respectively, as potassium dichromate for 9 weeks, (NTP 1996a, 1996b); however, no tests of renal function were performed. The available human and animal data provide strong evidence that the kidney is a target of chromium toxicity. A TTD_{RENAL} of 0.01 mg Cr(VI)/kg/day was derived using the NOAEL of 10 mg Cr(VI)/kg/day identified in the Diaz-Mayans et al. (1986) study and an uncertainty factor of 1,000 (10 for extrapolation from rats to humans, 10 for intrahuman variability, and 10 to extrapolate from an intermediate-duration study). The Kumar and Rana (1982, 1984) studies were not selected as the basis of the TTD because the potassium chromate was administered via gavage and there is some human evidence which suggests a higher absorption rate following bolus administration versus three divided dose administration (Kerger et al. 1997).

Cardiovascular Effects

Cardiovascular effects (e.g., cardiopulmonary arrest, hypoxic changes in myocardium, and progressive drop in cardiac output, heart rate and blood pressure) have been observed in humans following lethal ingestion of chromium(VI) (ATSDR 2000b). However, cardiovascular effects have not been observed in humans or animals exposed to nonfatal doses, suggesting that cardiovascular toxicity is not a target of concern. Thus, a TTD_{CARDIO} was not derived.

Hematological Effects

A series of intermediate-duration studies conducted by NTP (1996a, 1996b, 1997) have consistently shown slight dose-related decreases in mean corpuscular volume (MCV) and mean corpuscular hemoglobin (MCH) in rats and mice exposed to potassium dichromate in the diet for at least 9 weeks. The lowest identified LOAEL for these alterations, 7.8 mg Cr(VI)/kg/day, was found in F₁ female mice (NTP 1997); this study did not identify a NOAEL. This LOAEL and an uncertainty factor of 3,000 (3 for use of a minimal LOAEL, 10 for extrapolation from intermediate to chronic duration, 10 for interspecies extrapolation, and 10 for intrahuman variability) were used to derive a TTD_{HEMATO} of 0.003 mg Cr(VI)/kg/day.

Testicular Effects

Several animal studies have found reproductive effects in males orally exposed to 14–42 mg Cr(VI)/kg/day. These effects included decreases in testes, seminal vesicle, and preputial gland weights, decreased sperm counts, morphological sperm alterations, and alterations in sexual behavior (ATSDR 2000b). However, no histological or organ weight alterations were observed in rats and mice exposed to 9.8 or 32.2 mg Cr(VI)/kg/day as potassium dichromate in feed (NTP 1996a, 1996b) and no adverse effects were observed in a multigeneration reproductive study in which mice were exposed to 36.7 mg Cr(VI)/kg/day (NTP 1997). Although there are conflicting results, the available data suggest that chromium(VI) can adversely affect the male reproductive system. The lowest identified reliable LOAEL is 14 mg Cr(VI)/kg/day for decreased seminal vesicle and preputial gland weights in mice exposed to potassium dichromate in drinking water for 12 weeks (Elbetieha and Al-Hamood 1997). Application of a 3,000 uncertainty factor (3 for use of a minimal LOAEL, 10 for extrapolation from intermediate to chronic duration, 10 for interspecies extrapolation, and 10 for intrahuman variability) to this LOAEL yields a TTD_{TESTIC} of 0.005 mg Cr(VI)/kg/day. The Elbetieha and Al-Hamood (1997) study reported an increase in testes weight at 6 mg Cr(VI)/kg/day; however, this LOAEL was not selected for TTD derivation because this is the only study which found an increase in testes weight.

Summary (TTDs for Chromium(VI))

$TTD_{NEURO} = 0.01 \text{ mg Cr(VI)/kg/day } (1 \times 10^{-2} \text{ mg/kg/day})$

$TTD_{RENAL} = 0.01 \text{ mg Cr(VI)/kg/day } (1 \times 10^{-2} \text{ mg/kg/day})$

$TTD_{CARDIO} = \text{Not applicable}$

$TTD_{HEMATO} = 0.003 \text{ mg Cr(VI)/kg/day } (3 \times 10^{-3} \text{ mg/kg/day})$

$TTD_{TESTIC} = 0.005 \text{ mg Cr(VI)/kg/day } (5 \times 10^{-3} \text{ mg/kg/day})$